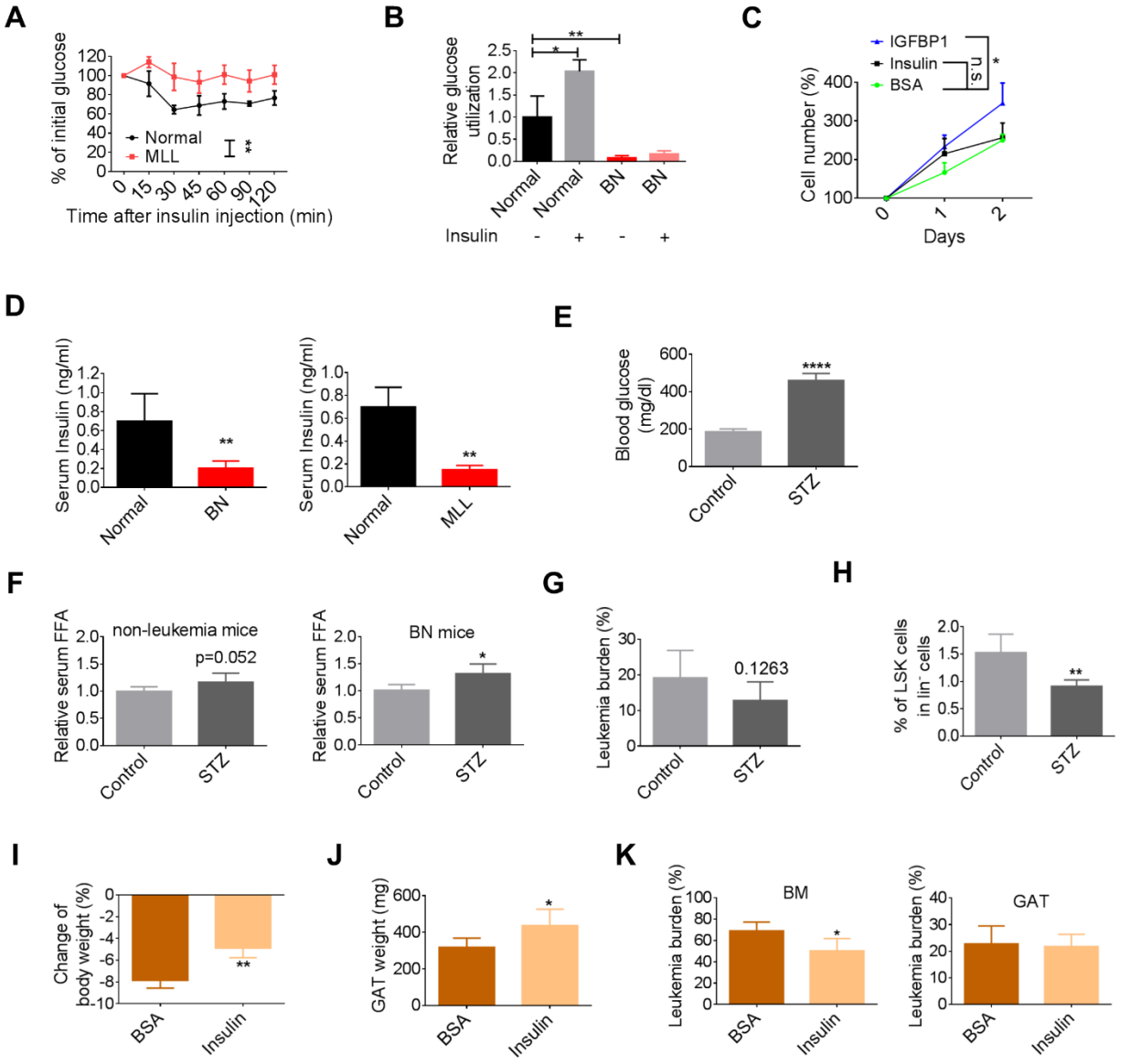

Figure S1, related to Figure 1. Leukemia induces IR and reduces serum insulin level. (A) ITT performed on normal and MLL mice (n=8). (B) Glucose utilization in soleus from normal and BN mice at the basal and insulin-stimulated conditions (n=3). (C) BN cells were sorted and cultured with the addition of insulin (1 ng/ml) or IGFBP1 (100 ng/ml) for two days. Cell number was counted each day (n=3). (D) Absolute value of fasting serum insulin in normal, BN and MLL mice (n=5). (E) Blood glucose levels in STZ-induced type 1 diabetic mice (n=5). (F) Serum FFAs in normal mice, non-leukemic diabetic mice, BN mice and diabetic BN mice (n=5). (G) BM leukemic burden in diabetic BN mice (n=5). (H) Percentage of LSK cells in the lineage$^-$ (lin$^-$) population from normal and non-leukemic diabetic BM (n=5). (I-J) Change of body weight (I) and GAT weight (J) in BN mice treated with insulin (n=6). (K) BM and GAT leukemic burden in MLL mice treated with insulin (n=5). Data are represented as mean ± SD.

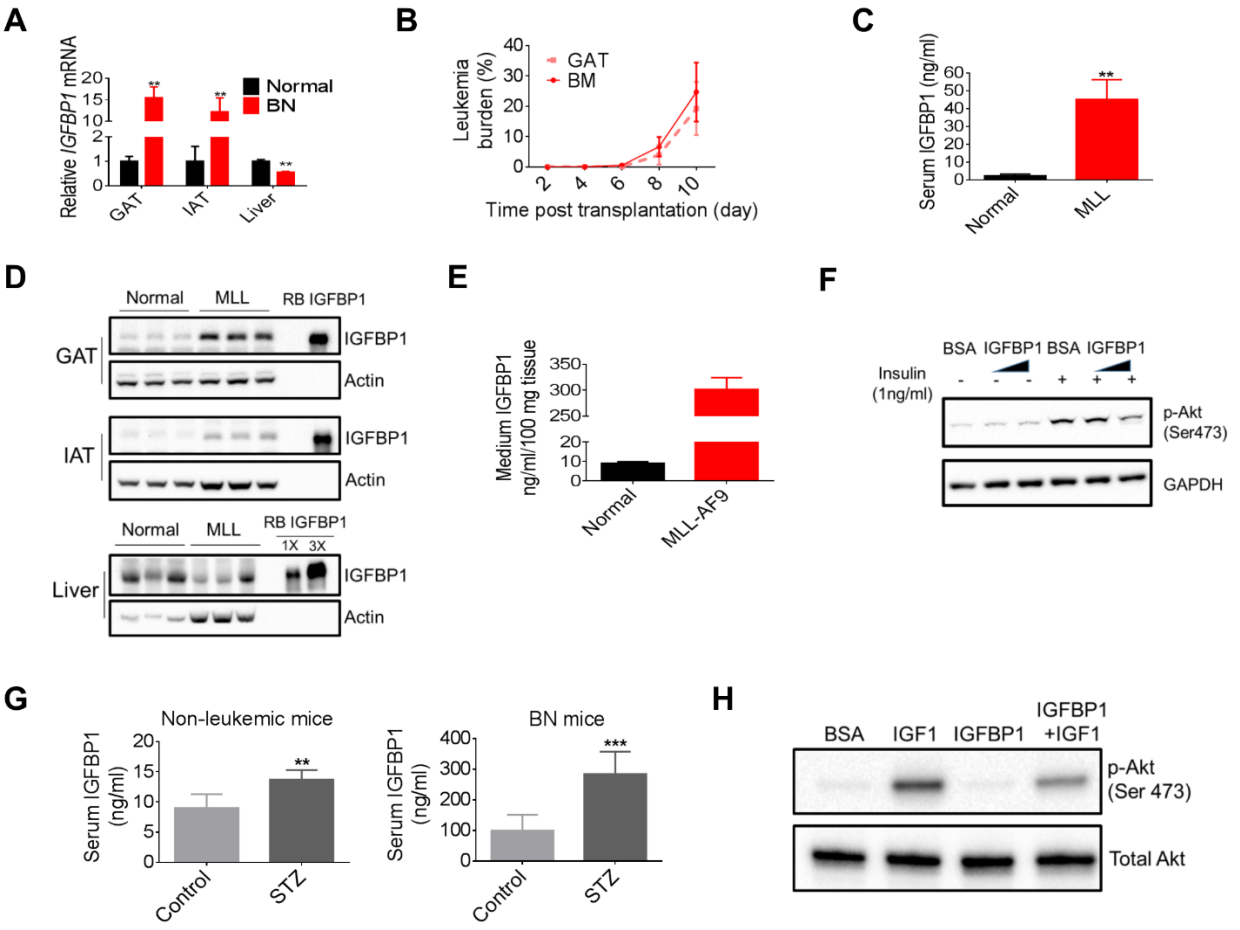

Figure S2, related to Figure 2. Leukemia induces IGFBP1 production. (A) *IGFBP1* mRNA levels in GAT, IAT and liver from normal and BN mice. (B) BM and GAT leukemic burden at different time points after leukemic transplantation (n=4). (C) Serum IGFBP1 in normal and MLL mice (n=5). (D) *IGFBP1* protein levels in GAT, IAT and liver from normal and MLL mice. Recombinant (RB) mouse IGFPB1 protein serves as a positive control. (E) IGFBP1 levels in CM from normal and MLL GAT. (F) Normal GAT explants were treated with insulin and different doses (20 ng/ml and 200 ng/ml) of IGFBP1 for 30 min. p-Akt level was determined at the basal and insulin-stimulated conditions. (G) Serum IGFBP1 levels in normal mice, non-leukemic diabetic mice, BN mice and diabetic BN mice (n=5). (H) Serum starved (1 hr) 3T3-L1 adipocytes were treated with IGF1 (100 ng/ml) or IGFBP1 (200 ng/ml) or IGF1 (100 ng/ml) plus IGFBP1 (200 ng/ml) for 30 min. Cells were harvest for detection of indicated protein. Data are represented as mean ± SD.

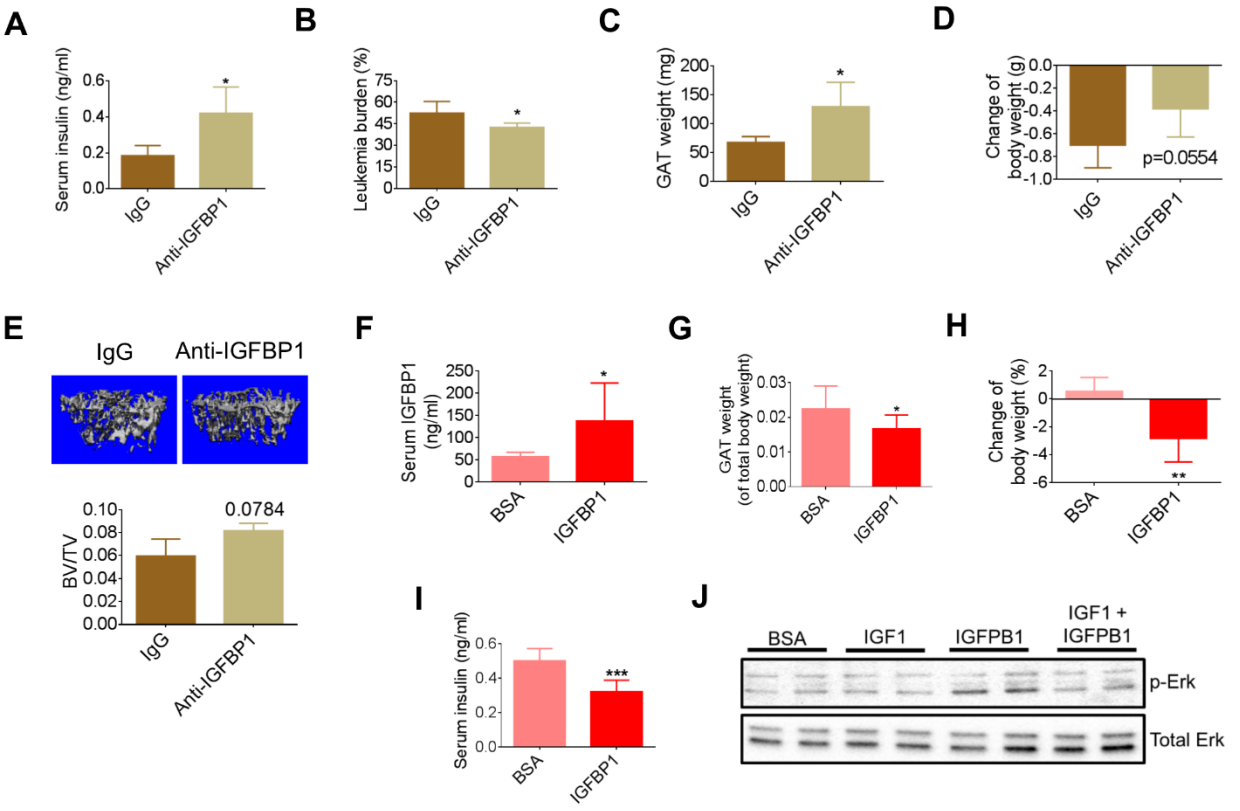

Figure S3, related to Figure 3. Modulation of IGFBP1 mediates leukemia growth in vivo. (A) Absolute value of fasting serum insulin in BN mice treated with anti-IGFBP1 antibody (n=5). (B-D) BM leukemic burden (B), GAT weight (C) and total body weight (D) in anti-IGFBP1 antibody treated BN mice (n=5). (E) Tibia trabecular bone mass was examined by Micro-CT (n=4). (F-I) Serum IGFBP1 (F), GAT weight (G), total body weight (H) and absolute value of fasting serum insulin (I) in IGFBP1-preconditioned BN mice (n=5). (J) BN cells were treated with IGFBP1 (200 ng/ml) or IGF1 (100 ng/ml) or IGFBP1 (200 ng/ml) plus IGF1 (100 ng/ml) for 30 min. Cells were harvested for detection of indicated protein. Data are represented as mean ± SD.

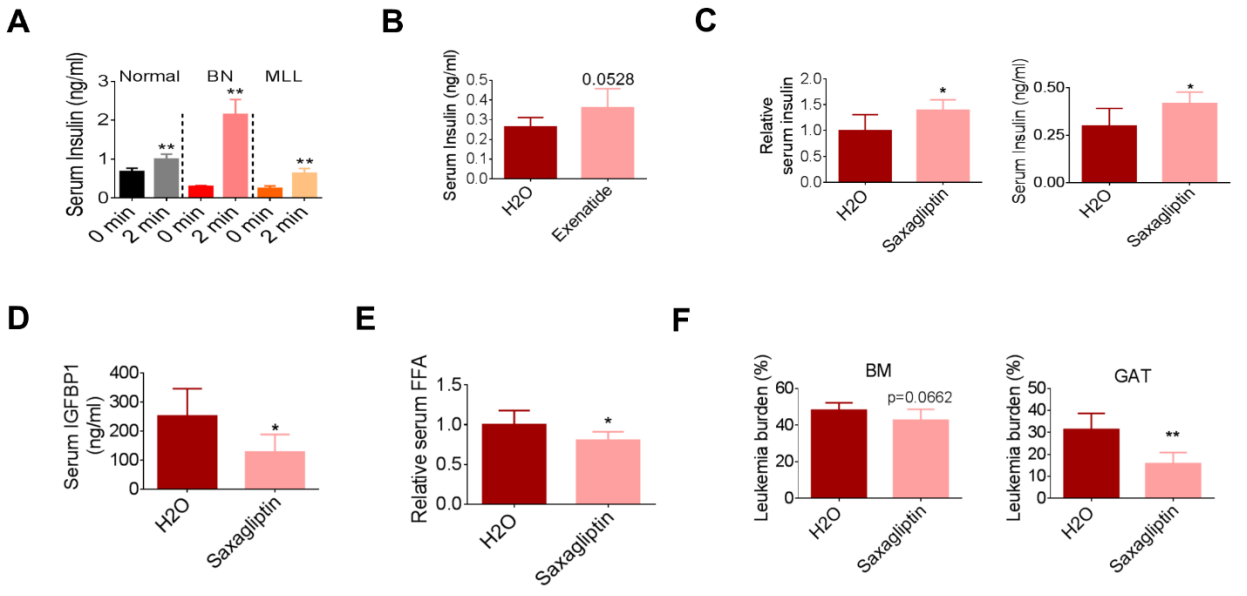

Figure S4, related to Figure 4. Inhibition of DPP4 impedes leukemia progression. (A) Absolute value of fasting serum insulin in normal, BN and MLL mice challenged with glucose bolus (n=4). (B) Absolute value of fasting serum insulin in BN mice treated with Exenatide. (C-F) Fasting serum insulin (C), serum IGFBP1 (D), serum FFAs (E), BM and GAT leukemic burden (F) in Saxagliptin treated BN mice (n=5). Data are represented as mean ± SD.

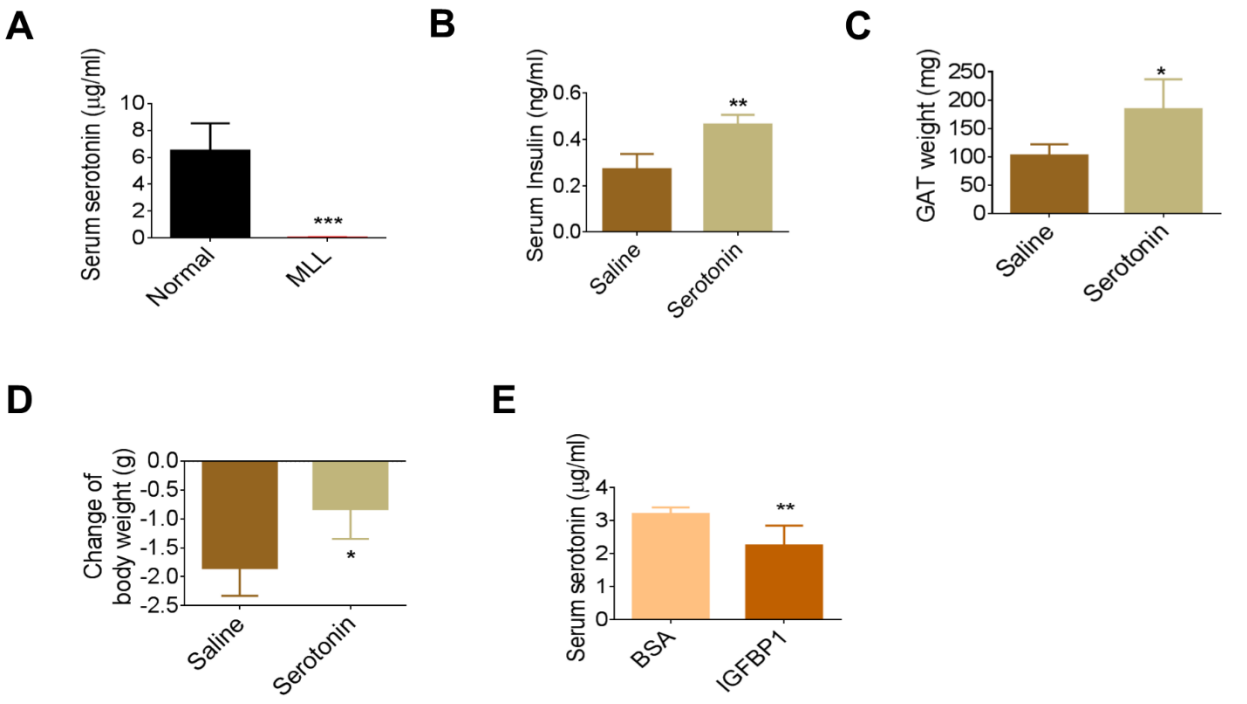

Figure S5, related to Figure 5. Serotonin supplementation reduces leukemic burden. (A) Serum serotonin in normal and MLL mice (n=4). (B) Absolute value of fasting serum insulin in BN mice treated with serotonin (n=5). (C-D) GAT weight (C) and change of body weight (D) in serotonin treated BN mice (n=5). (E) Serum serotonin levels in IGFBP1-preconditioned BN mice (n=5). Data are represented as mean ± SD.

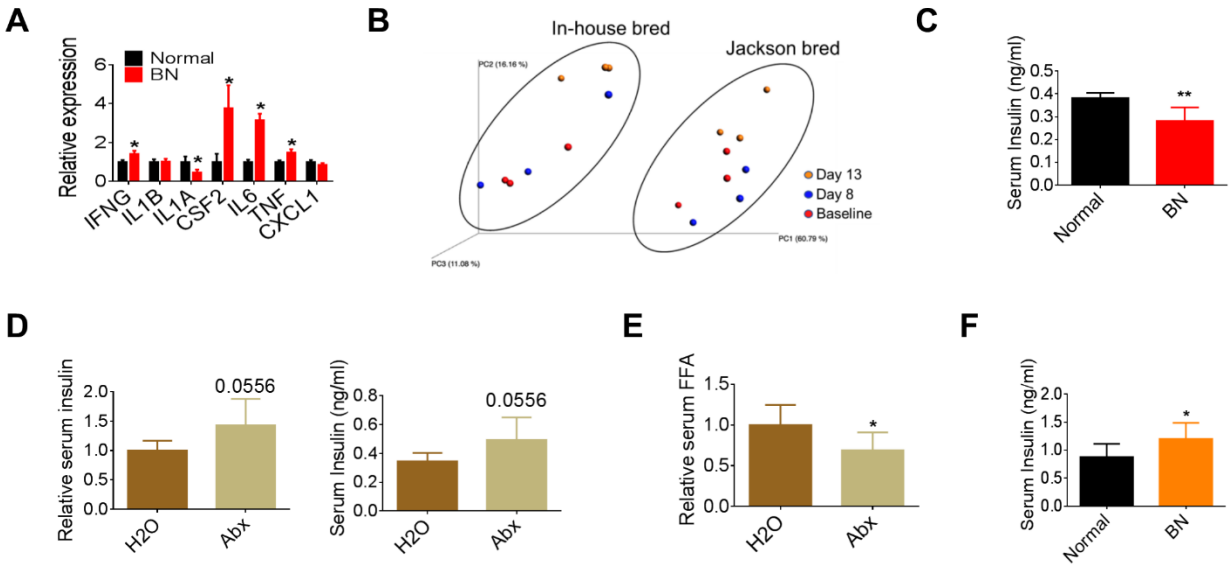

Figure S6, related to Figure 6. Leukemia associated microbiota facilitates disease progression. (A) Gene expression of inflammatory cytokines in the colon tissues from normal and BN mice. (B) PCoA of the weighted UniFrac distance matrix created with QIIME 1.9. Samples from mice bred in the Jackson lab and in-house bred mice clustered apart as indicated (Figure 6B showing results from in-house bred mice). Microbial communities were analyzed at baseline (normal), 8, and 13 days post leukemic transplantation. Each sample represents data from fecal samples of 5 mice pooled prior to DNA extraction. Mice from 3 cages were sampled. The two breeding populations showed overall community-level differences and similar longitudinal differences. Baseline and day 8 samples show minor change within a cohort, but day 13 shows a distinct change in community composition for both breeding populations. (C) Absolute value of fasting serum insulin in BN mice transplanted with fecal materials from normal or BN mice (n=7). (D-E) Fasting serum insulin (D) and serum FFAs (E) in Abx treated BN mice (n=5). (F) Absolute value of fasting serum insulin in non-leukemic mice transplanted with fecal materials from normal or BN mice (n=7). Data are represented as mean ± SD.

Table S1, related to Figure 6. Composition of taxonomy in normal and BN fecal materials.

Legend	Taxonomy	Normal	BN	p value
	Unassigned;Other;Other;Other;Other;Other	0.3333	0.0000	0.0194
	k__Bacteria;p__Actinobacteria;c__Actinobacteria;o__Bifidobacteriales;f__Bifidobacteriaceae;g__Bifidobacterium	0.3667	0.0000	0.00625
	k__Bacteria;p__Actinobacteria;c__Coriobacteriia;o__Coriobacteriales;f__Coriobacteriaceae;g__Adlercreutzia	0.1667	0.0000	0.00037
	k__Bacteria;p__Bacteroidetes;c__Bacteroidia;o__Bacteroidales;f__Bacteroidaceae;g__Bacteroides	0.1000	0.1000	0.28689
	k__Bacteria;p__Bacteroidetes;c__Bacteroidia;o__Bacteroidales;f__Porphyromonadaceae;g__Parabacteroides	0.1000	0.1000	0.87946
	k__Bacteria;p__Bacteroidetes;c__Bacteroidia;o__Bacteroidales;f__Rikenellaceae;g__	5.6000	5.9000	0.77491
	k__Bacteria;p__Bacteroidetes;c__Bacteroidia;o__Bacteroidales;f__S24-7;g__	30.4667	24.5000	0.0015
	k__Bacteria;p__Firmicutes;c__Bacilli;o__Lactobacillales;f__Lactobacillaceae;g__Lactobacillus	0.1333	0.0000	0.00039
	k__Bacteria;p__Firmicutes;c__Bacilli;o__Turicibacterales;f__Turicibacteraceae;g__Turicibacter	2.4333	0.0333	0.0016
	k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__;g__	28.4000	33.8000	0.0382
	k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Christensenellaceae;g__	0.1000	0.1667	0.04884
	k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Clostridiaceae;g__	0.1000	0.0333	0.1161
	k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Clostridiaceae;g__Clostridium	0.2333	0.1333	0.01429
	k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Dehalobacteriaceae;g__Dehalobacterium	0.1000	0.1000	1.0000
	k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Lachnospiraceae;Other	0.1000	0.1000	1.0000
	k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Lachnospiraceae;g__	4.7000	5.3000	0.97114
	k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Lachnospiraceae;g__Anaerostipes	0.1000	0.0000	0.01313
	k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Lachnospiraceae;g__Coprococcus	0.9667	0.7000	0.37587
	k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Lachnospiraceae;g__Dorea	0.2667	0.1667	0.21699
	k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Lachnospiraceae;g__[Ruminococcus]	0.4333	0.4667	0.76115
	k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Peptostreptococcaceae;g__	0.0667	0.0000	0.52495
	k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Ruminococcaceae;Other	1.9333	2.3333	0.00216
	k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Ruminococcaceae;g__	2.5333	2.4667	0.80353
	k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Ruminococcaceae;g__Oscillospira	9.7667	10.9000	0.36929
	k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Ruminococcaceae;g__Ruminococcus	3.8333	3.4333	0.17142
	k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__[Mogibacteriaceae];g__	0.1000	0.0333	0.00022
	k__Bacteria;p__Firmicutes;c__Erysipelotrichi;o__Erysipelotrichales;f__Erysipelotrichaceae;g__	0.2333	0.1333	0.21542
	k__Bacteria;p__Firmicutes;c__Erysipelotrichi;o__Erysipelotrichales;f__Erysipelotrichaceae;g__Allobaculum	0.8333	0.0000	0.00004
	k__Bacteria;p__Proteobacteria;c__Gammaproteobacteria;o__Enterobacteriales;f__Enterobacteriaceae;g__Proteus	0.0667	0.0667	0.8248
	k__Bacteria;p__Tenericutes;c__Mollicutes;o__Anaeroplasmatales;f__Anaeroplasmataceae;g__Anaeroplasma	1.1667	0.8667	0.20211
	k__Bacteria;p__Tenericutes;c__Mollicutes;o__RF39;f__;g__	2.5667	2.4333	0.01661
	k__Bacteria;p__Verrucomicrobia;c__Verrucomicrobiae;o__Verrucomicrobiales;f__Verrucomicrobiaceae;g__Akkermansia	1.6667	5.6333	0.00873

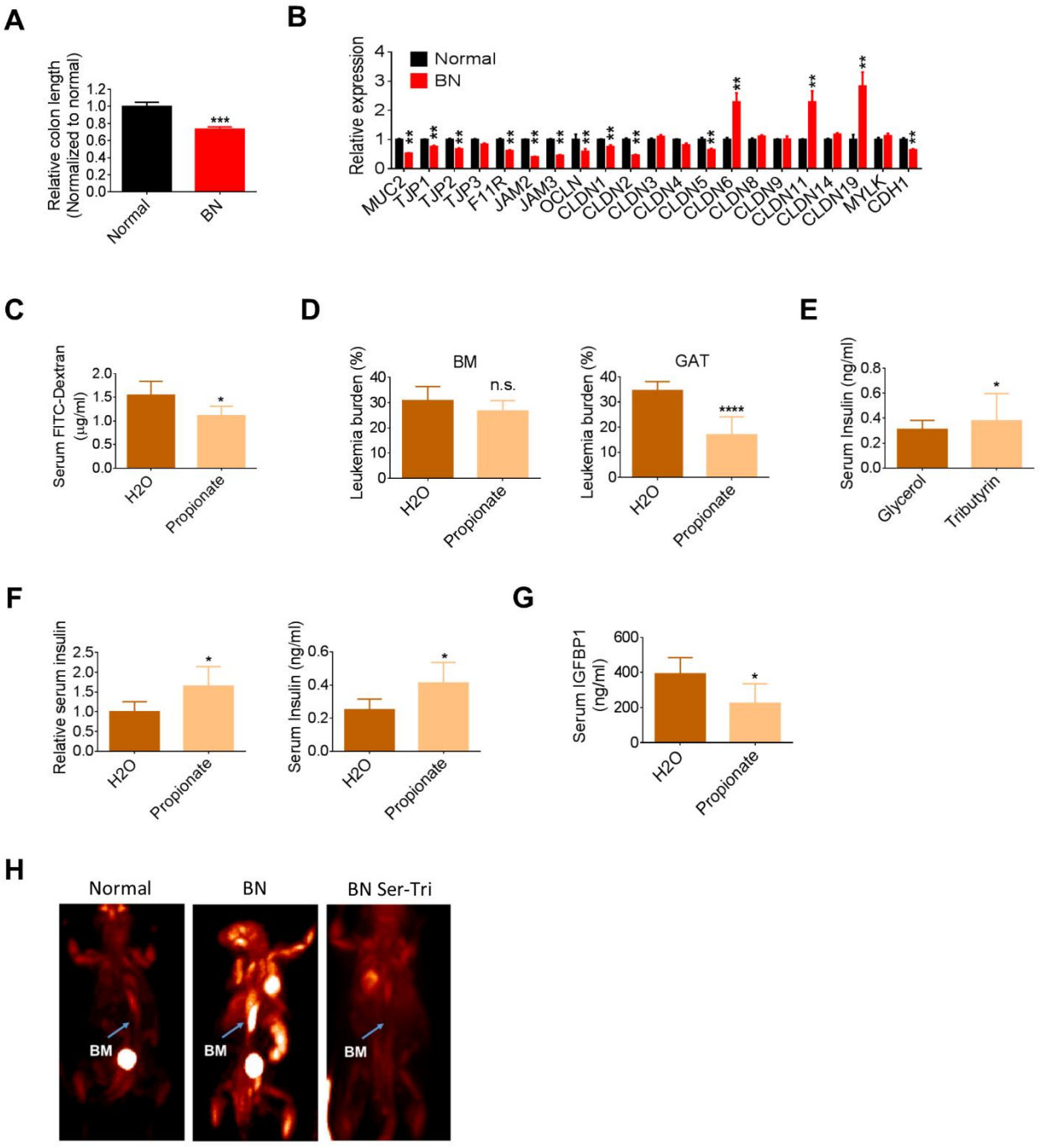

Figure S7, related to Figure 7. Propionate supplementation reduces GAT leukemic burden. (A) Length of colon tissues from normal and BN mice (n=4). (B) Expression of genes involved in barrier function in colon tissues from normal and BN mice. (C-D) Serum FITC-Dextran levels (C), BM and GAT leukemic burden (D) in propionate treated BN mice (n=6). (E) Absolute value of fasting serum insulin in BN mice treated with tributyrin (n=6). (F-G) Fasting serum insulin (F) and serum IGFBP1 (G) in propionate treated BN mice (n=6). (H) Raw representative images of ^{18}F-fluorodeoxyglucose (FDG) uptake in the bone marrow (BM) by PET-CT imaging in normal mice, untreated BN mice, and BN mice treated with Ser-Tri therapy. Data are represented as mean ± SD.

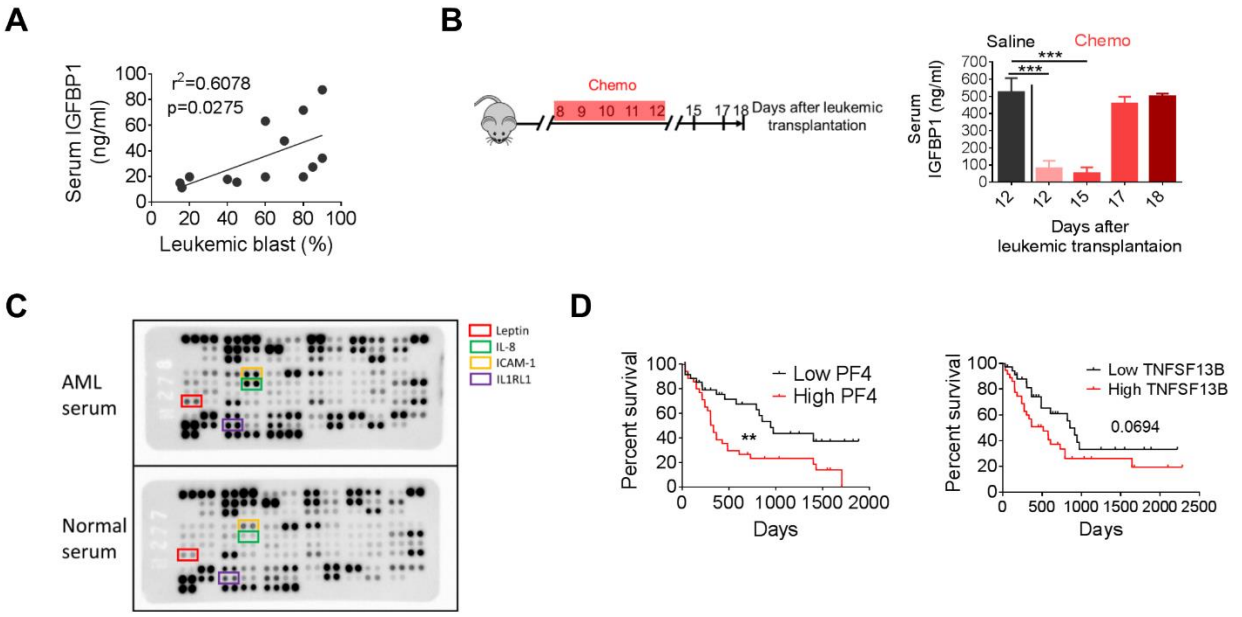

Figure S8, related to Figure 8. Human leukemia induces insulin resistance. (A) Correlation between leukemic blast counts and serum IGFBP1 in AML patients. (B) Serum IGFPB1 level in saline treated BN mice, BN mice just finished chemotherapy and BN mice relapsed from chemotherapy (n=5). Data are represented as mean ± SD. (C) Cytokine array (longer exposure) performed on serum samples from normal controls and AML patients. (D) Survival curve for AML patients with high and low expression of TNFSF13B and PF4 (n=37).

Table S2, related to STAR Methods. Primers used in this paper.

Name	Sequence	Name	Sequence
Mouse TJP1 FW	GAGCGGGCTACCTTACTGAAC	Mouse F11R FW	AGTGGAAGTTCGTCCAAGGC
Mouse TJP1 REV	GTCATCTCTTTCCGAGGCATTAG	Mouse F11R REV	ACTCGGTCCGCATAGGGAG
Mouse TJP2 FW	ATGGGAGCAGTACACCGTGA	Mouse JAM2 FW	GTGCCCACTTCTGTTATGACTG
Mouse TJP2 REV	TGACCACCCTGTCATTTTCTTG	Mouse JAM2 REV	TTCCCTAGCAAACTTGTGCCA
Mouse TJP3 FW	AGGTCGATCATGGGGTGAG	Mouse JAM3 FW	CTGCGACTTCGACTGTACG
Mouse TJP3 REV	CCAGACCGTTGGCTTCAGAT	Mouse JAM3 REV	TTCGGTTGCTGGATTTGAGATT
Mouse OCLN FW	TTGAAAGTCCACCTCCTTACAGA	Mouse MYLK FW	TTCCAGGGGAGACTCGTCC
Mouse OCLN REV	CCGGATAAAAAGAGTACGCTGG	Mouse MYLK REV	CATCTGCCCTTCTTTGACCAC
Mouse CLDN1 FW	GGGGACAACATCGTGACCG	Mouse CLDN 4 FW	TGGAGGACGAGACCGTCAA
Mouse CLDN1 REV	AGGAGTCGAAGACTTTGCACT	Mouse CLDN 4 REV	CACGGGCACCATAATCAGCA
Mouse CLDN2 FW	CAACTGGTGGGCTACATCCTA	Mouse CLDN 8 FW	GCAACCTACGCTCTTCAAATGG
Mouse CLDN2 REV	CCCTTGGAAAAGCCAACCG	Mouse CLDN8 REV	TTCCCAGCGGTTCTCAAACAC
Mouse CLDN3 FW	ACCAACTGCGTACAAGACGAG	Mouse CLDN14 FW	GTCCTGGACCACGAATGACG
Mouse CLDN3 REV	CAGAGCCGCCAACAGGAAA	Mouse CLDN14 REV	GGCCGATTTCAAACTTCATGC
Mouse CLDN5 FW	GCAAGGTGTATGAATCTGTGCT	Mouse CLDN19 FW	GCCCTGGACGGTCATATCC
Mouse CLDN5 REV	GTCAAGGTAACAAAGAGTGCCA	Mouse CLDN19 REV	TTACTGTCTCCAACCCGAGTG
Mouse CLDN6 FW	ATGGCCTCTACTGGTCTGCAA	Mouse CLDN11 FW	ATGGTAGCCACTTGCCTTCAG
Mouse CLDN6 REV	GCCAACAGTGAGTCATACACCTT	Mouse CLDN11 REV	AGTTCGTCCATTTTTCGGCAG
Mouse CLDN9 FW	TGTGGCCCAAGTGGTATGG	Mouse ACTB FW	GTGACGTTGACATCCGTAAAGA
Mouse CLDN9 REV	GCGGTGAGTACGATACGGG	Mouse ACTB REV	GCCGGACTCATCGTACTCC
Mouse IGFBP1 FW	CTGCCAAACTGCAACAAGAATG	Mouse GAPDH FW	AGGTCGGTGTGAACGGATTTG
Mouse IGFBP1 REV	GGTCCCCTCTAGTCTCCAGA	Mouse GAPDH REV	GGGGTCGTTGATGGCAACA
Mouse REG3G FW	ATGCTTCCCCGTATAACCATCA	Mouse LCN2 FW	TGGCCCTGAGTGTCATGTG
Mouse REG3G REV	GGCCATATCTGCATCATACCAG	Mouse LCN2 REV	CTCTTGTAGCTCATAGATGGTGC
Mouse REG3B FW	ACTCCCTGAAGAATATACCCTCC	Mouse S100A8 FW	AAATCACCATGCCCTCTACAAG
Mouse REG3B REV	CGCTATTGAGCACAGATACGAG	Mouse S100A8 REV	CCCACTTTTATCACCATCGCAA
Moyse IFNG FW	ATGAACGCTACACACTGCATC	Mouse S100A9 FW	ATACTCTAGGAAGGAAGGACACC
Mouse IFNG REV	CCATCCTTTTGCCAGTTCCTC	Mouse S100A9 REV	TCCATGATGTCATTTATGAGGGC
Mouse MPO FW	AGTTGTGCTGAGCTGTATGGA	Mouse MUC2 FW	ATGCCCACCTCCTCAAAGAC
Mouse MPO REV	CGGCTGCTTGAAGTAAAACAGG	Mouse MUC2 REV	GTAGTTTCCGTTGGAACAGTGAA
Mouse IL1B FW	GCAACTGTTCCTGAACTCAACT	Mouse CSF2 FW	GGCCTTGGAAGCATGTAGAGG
Mouse IL1B REV	ATCTTTTGGGGTCCGTCAACT	Mouse CSF2 REV	GGAGAACTCGTTAGAGACGACTT
Mouse IL1A FW	CGAAGACTACAGTTCTGCCATT	Mouse IL6 FW	TAGTCCTTCCTACCCCAATTTCC
Mouse IL1A REV	GACGTTTCAGAGGTTCTCAGAG	Mouse IL6 REV	TTGGTCCTTAGCCACTCCTTC
Mouse CXCL1 FW	ACTGCACCCAAACCGAAGTC	Mouse TNF FW	CCCTCACACTCAGATCATCTTCT
Mouse CXCL1 REV	TGGGGACACCTTTTAGCATCTT	Mouse TNF REV	GCTACGACGTGGGCTACAG